PREDICTORS AND IMPACT ON OUTCOME OF REFRACTORY STATUS EPILEPTICUS

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CERTIFICATE

This is to certify that the dissertation titled, **"Predictors and impact on the outcome of refractory status epilepticus"** submitted by Dr. R Pradeep Raj, to the Faculty of Paediatrics, The Tamilnadu Dr. M.G.R Medical University, Chennai, in partial fulfillment of the requirements for the award of M.D. Degree (Paediatrics) is a bonafide research work carried out by him under our direct supervision and guidance, during the academic year 2007-2010

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CONTENTS

INTRODUCTION

Status epilepticus (SE) is a frequent neurological emergency . The incidence of SE has a bimodal distribution with peaks in children aged less than a year and the elderly[1].Although conventional antiepileptic drugs (AED) can terminate SE in most cases, a substantial minority of patients develop medically refractory status epilepticus (RSE).

Status epilepticus is defined as a continuous convulsion lasting longer than 30 minutes or the occurrence of serial convulsions between which there is no return of consciousness[2]. Mild degrees of pure hypoxia causes impaired judgement,inattentiveness,motor incoordinationand at times,euphoria. With hypoxic ischemia, consciousness is lost within seconds. If circulation is restored within 3-5 minutes, full recovery may occur, but if hypoxic-ischemia lasts beyond 3-5 minutes some degree of permanent cerebral damage is the rule[3]. Status Epilepticus is common in childhood, and the reported current mortality is in the range of 4-6% [4].

The evolution of a prolonged seizure into Status Epilepticus is associated with increased morbidity and mortality. Hypoxia is currently thought to be responsible for most of the complications seen in Status Epilepticus. [5].

REFRACTORY STATUS EPILEPTICUS (RSE):

Although the entity of RSE is widely recognized and discussed, a standard definition has not yet been evolved and is usually defined as seizure activity that continues after first- and second-line therapy has failed.[6]Such patients are considered to be in Refractory Status Epilepticus and escalation of therapy with administration of barbiturate or non-barbiturate anesthetic agent is then recommended with the therapeutic endpoint of achieving seizure control, electrical silence or both [7]. These patients require management in pediatric intensive care unit, with continuous cardiorespiratory and electro-encephalographic monitoring along with the aggressive therapy to control seizures

The optimal management of such patients remains unclear and large, controlled studies comparing the various agents are lacking. Generalized status epilepticus is refractory to standard anticonvulsant therapy in at least 9% of patients and additional intervention is required [8 ,9].

The significant morbidity and mortality in refractory status epileptics is due to the nature of underlying illness and sustained seizure activity as well as the toxicity of concurrent treatment modalities. Many studies have come out which suggest that continuous intravenous infusion of midazolam in safe and effective therapy for refractory status epilepticus. On the other hand studies using other drugs e.g. Pentobarbital, propofol, ketamine anesthesia and paraldehyde were shown to be associated with many

disadvantages due to their side effects.

Though refractory status epilepticus is a life threatening condition, there is no standard drug or standard protocol for its treatment and also treatment varies from institution to institution. Many drugs are being tried and there is no fixed consensus arrived as which would be the best in children for early control of seizures and having minimal side effects. Very few studies have been done in India and abroad on Refractory Status Epilepticus, so, the data on the clinical profile and treatment modalities and their effectiveness is also limited. Moreover, the drugs and the doses at which refractory status epilepticus was controlled on western population may not be same in our children.

Important causes of status epilepticus [10]: The important causes can be broadly divided into:

1. **Acute Causes -** CNS Infections (Meningitis / Meningo Encephalitis)
   Febrile Convulsions
   Vascular Episodes
   Trauma
   Metabolic Problems and
   Poisonings

2. **Static Causes-**

Status Epilepticus can occur as a first manifestation of epilepsy or during the course of epilepsy with or without an underlying neurological disorder. In known epilepticus, drug default or sudden withdrawal of antiepileptics or undercurrent infections and stress may predispose to status epilepticus.

3. **Degenerative or Progressive Neurological Conditions**

After a single episode of status epilepticus, subsequent episodes are more common with risk of recurrence of 17% for a second episode and 5% for further attacks [11]. In relation to premorbid state, the recurrence risk for status epilepticus for those with prior neurological abnormalities is about 50% and in those who are neurologically normal, it is 3% [11].

If status epilepticus could not be controlled by front-line anticonvulsants (Diazepam, lorazepam, phenytoin and phenobarbitone) and seizures become refractory then the following reasons should be reassessed systematically [12].

1. Adequacy of drug therapy.
2. Initiation of appropriate maintenance antiepileptic therapy
3. Failure to identify and treat the underlying causes e.g. Acutve progressive cerebral disorders and cerebral infections.
4. Misdiagnosis of pseudo status as status epilepticus
5. Underlying metabolic disorder or structural defects

PATHOPHYSIOLOGY OF STATUS EPILEPTICUS (SE):

SE refers to a condition in which there is a failure of the "normal" factors to terminate a typical seizure. y-Aminobutyric acid (GABA) receptor-mediated inhibition may be responsible for the normal termination of a seizure. In addition, the activation of the N-methyl-D aspartate (NMDA) receptor by the excitatory neurotransmitter glutamate may be required for the propagation of seizure activity.[13] SE that is refractory to treatment may be the result of several processes and has been attributed to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive NMDA excitatory receptor-mediated transmission.[14] In experimental models, resistance to both benzodiazepines and barbiturates develops during prolonged seizures and it has been hypothesized that prolonged seizure activity alters the structure and/or function of GABAA receptors.[15] SE induced neuronal death is morphologically necrotic and is initiated by excessive glutamate release, which activates postsynaptic NMDA receptors and triggers receptor-mediated calcium influx (excitotoxicity). This results in a cascade of events and cell death.[16] The alterations in inhibitory and excitatory pathways have important implications for the pharmacological management of SE. Another important aspect of self-sustaining SE is the progressive, time-dependent development of pharmacoresistance. Currently recommended agents acts primarily through the GABA A receptor and have been shown to become less effective in SE of longer duration. Drugs shown to be effective in RSE act at different receptor sites other

than benzodiazepine receptor site, propofol acts at a site distinct from the benzodiazepine and barbiturate binding sites, isoflurane acts by potentiation of inhibitory postsynaptic GABA A receptor-mediated currents, although effects on thalamo-cortical pathways also have been implicated.[17]

COMPLICATIONS OF STATUS AND REFRACTORY STATUS EPILEPTICUS:

Systemic changes and complications of status epilepticus and protean with the involvement of all organ systems and these undoubtedly contribute to the ultimate mortality seen in patients with Status Epilepticus and Refractory Status epilepticus. As the duration of status epilepticus progresses, there is systemic alteration, with worsening of general clinical state. The final stages are characterized by respiratory compromise, hypotension, hypothermia and ongoing epileptiform paroxysms without motor accompaniments.

The table given below lists the various complications [4]:

1. Interictal coma
2. Cumulative anoxia- cerebral and systemic
3. Cardiovascular complications – Tachycardia, Bradycardia, cardiac arrest, hypertension, cardiac failure, shock.
4. Respiratory system failure- Apnoea, Cheyne-stokes breathing, aspiration, pneumonia, tachypnea, neurogenic pulmonary edema, pulmonary embolism,

cyanosis, respiratory acidosis.

5. Renal failure- Oliguria, uremia, acute tubular necrosis, rhabdomyolysis.
6. Autonomic disturbances – Hyperpyrexia, sweating, vomiting, hypersecretion, airway obstruction.
7. Metabolic and Biochemical abnormalities – Acidosis (Metabolic, lactic acidosis), hyper and hyponatremia, hyperkalemia, hypoglycemia, hepatic failure, dehydration, acute pancreatitis.
8. Infections- pulmonary, bladder
9. Others – Disseminated intravascular coagulation, multiple organ dysfunction, fractures, thrombophlebitis.

INVESTIGATIONS:

A battery of investigations will be required not only for identifying the underlying etiology but also to monitor the alterations in the metabolic parameters during status epilepticus. The investigations for cause of status are guided by thorough history and clinical examination of the child. The following are the investigations, which are helpful in the accurate diagnosis and management of the child.

1. Complete blood counts, Blood Sugar, electrolytes, Serum calcium, phosphorus, magnesium levels
2. Mantoux test, resting gastric juice for acid fast bacilli toxicology screening.
3. Serum creatinine, lactate and ammonia levels.

4. Liver function tests, blood culture
5. Anticonvulsant levels, urine analysis and toxicology
6. Lumbar puncture and analysis of fluid for protein, sugar, Grams stain and culture
7. Arterial blood gas analysis.
8. X-ray chest, CT scan brain, MRI brain
9. Continuous electro encephalographic monitoring.

INITIAL EVALUATION:

After performing a rapid but thorough cardiopulmonary assessment and stabilizing the airway, breathing and circulation, a detailed physical and neurological examination should be carried out to pick up the probable etiology and complications of seizures.

Assess for evidence of trauma; signs of raised intracranial pressure like papilloedema, bulging anterior frontenalle or focal neurological deficit; manifestations of sepsis or meningitis. Look for Kussmaul breathing and dehydration suggestive of metabolic acidosis or irregular respirations signifying brain stem dysfunction; evidence of failure to thrive, a peculiar body odor or abnormal hair pigmentation that suggests an inborn error of metabolism and constricted or dilated pupils suggesting a toxin or drug as the cause of status epilepticus[2].

MANAGEMENT:

Prompt and aggressive management of status epilepticus is essential; because it is

shown that there is progressive loss in the ability of antiepileptic drugs to control the severe seizures of status epilepticus. This time dependant development of pharmacoresistant status epilepticus is extremely important in the management of status epilepticus [18].

The main goals of management of status epilepticus are to:

1. Support vital function
2. Terminate seizure activity as fast possible
3. Prevent recuurence of seizures

SUMMARY OF EMERGENCY MANAGEMENT OF STATUS EPILEPTICUS

Immediate

Airway - Protect airway – use 100% oxygen and endotracheal tube if necessary

Breathing - Support and use muscle relaxant if necessary

Circulation - Maintain adequate perfusion and normal blood pressure- support if necessary

Establish secure intravenous line.

Draw - Laboratory samples

Administer - 2 ml of 25% dextrose per kilogram intravenous

Anticonvulsants

First Line - Diazepam (0.2 mg/kg) IV

(0-10 min) (or)

Lorazepam (0.1 mg/kg) IV given over 30-60 sec. (Repeat same dose after 10 min. if seizures are not controlled).

Second Line- Phenytoin 20 mg/kg IV infusion

in 20 ml of Normal saline over 20 minutes

(Not to exceed 1 mg/kg/mt)

↓

Seizures not controlled

↓

Phenytoin 10mg/kg infusion half loading dose

↓

Seizures are not controlled

↓

Phenobarbitone loading dose 20 mg/kg slow IV infusion

(Intubate)

↓

Seizures not controlled

↓

Refractory Status Epilepticus

MANAGEMENT OF REFRACTORY STATUS EPILEPTICUS

RSE requires more aggressive treatment and however, the optimal treatment has not been defined. Patients should be treated in intensive care unit, as artificial ventilation and hemodynamic support is required. These patients generally require intravenous fluids and vasopressors to treat hypotension associated with high dose intravenous use of anesthetic agents. In a third of adults in SE, arterial pH falls below 7;[19] the main contribution to this change is lactic acidosis from skeletal muscle,[20] which responds well to oxygen and control of convulsive activity. Mild acidosis might be an anticonvulsant and neuroprotective. The usual practice is to treat with bicarbonate if the patient is hypotensive and arterial pH if it is < 7 due to metabolic acidosis. Control of hypothermia is neuroprotective.[21]

Pharmacological treatment

To date, no randomized controlled trials have been done for SE refractory to first- and second-line therapy. The most experience exists with continuous infusion (cIV) of pentobarbital, midazolam and propofol,[22]. The best comparative information comes from the systematic review by Claassen and colleagues. No difference was found in mortality among the groups treated with cIV propofol, cIV midazolam and cIV pentobarbital. Mortality was related to patient's age and duration of SE rather than AED choice. A recent retrospective study investigated the effect on RSE prognosis of various coma-inducing pharmacologic options. Mortality and likelihood of the patient's condition returning to clinical baseline at discharge did not differ significantly among

the three arms, barbiturates (pentobarbital and phenobarbital), propofol and midazolam. This study did not find any evidence for mortality related to propofol infusion syndrome.

Traditionally, barbiturates such as pentobarbital or thiopental have been used to terminate RSE, inducing coma and EEG suppression.[23],[24] However their effectiveness has not been studied systematically. In a systematic review of 109 adult patients with RSE who were treated with pentobarbital 8% experienced acute failure; 12%, breakthrough seizures; 43%, withdrawal seizures within 48 hours; and 8%, refractory hypotension during the therapy. EEG burst suppression or complete suppression has been achieved more frequently in episodes treated with barbiturates. Pentobarbital use is also often accompanied by prolonged sedation and life threatening infections. Episodes treated with barbiturates were associated with significantly longer hospital stay for surviving patients compared with episodes in which barbiturates were not used.

Superior pharmacokinetics and favorable adverse effect profile makes propofol the drug of choice. The two main advantages of propofol are a rapid onset and short duration of action. Propofol is a GABAA agonist that suppresses seizure activity via GABA-mediated inhibition of neuronal firing. Other mechanisms of action include inhibition of N-methyl-D aspartate receptor and modulation of calcium influx through slow calcium ion channels. The safety of propofol was further supported in recent retrospective series both in adults[22] and children. A prospective study has also shown its efficacy in RSE.[25] In a retrospective series

by Rossetti *et al*[40] in which 27 patients who failed to intravenous clonazepam and phenytoin therapy were induced into burst suppression pattern on cEEG with cIV propofol at a dose of 2.1 to 13 mg/kg/h for 1 to 9 days while continuing clonazepam infusion. RSE was successfully treated with propofol in 21 (67%) episodes. Seven deaths (23%) wee reported and none were attributable directly to propofol use and no patient experienced propofol infusion syndrome. In pediatric RSE also propofol has been shown to be a safe and effective drug, 14 (64%) of the 22 episodes could be adequately controlled. Two patients who were successfully treated with propofol died and the death was related to the underlying etiology and not to the use of propofol. However propofol may cause metabolic acidosis and cardiovascular collapse with prolonged use in children and deaths have been reported the propofol infusion syndrome.[26] Propofol should therefore be used with caution in children, ideally for short time only and the infusion rate should not exceed 67 ug/kg/min.[27] In a prospective study the quality of burst suppression was unsatisfactory in most patients. The maintenance of continuous burst suppression is difficult and vigilant titrating of dosage of propofol is necessary under EEG monitoring.[25]

Midazolam is an effective, short acting benzodiazepine that when given as an infusion has an efficacy in RSE, including at sub-anesthetic doses. It has the advantages of rapid onset of activity and greater water solubility, avoiding the problem of metabolic acidosis from the propylene glycol vehicle of other

benzodiazepines and barbiturates. Midazolam binds to GABAA receptors and augments GABAergic transmission, there by imparting anticonvulsant and sedative-hypnotic properties.[28] Duration of antiepileptic effects is minutes to hours. The elimination half-life is 1.5 to 3.5 hours initially. With prolonged use, there may be tolerance, tachyphylaxis and significant prolongation of half-life, up to days.[29] After 24-48 h, the dose of the drug must often be increased severalfold to maintain seizure control. Clinical experience with midazolam for RSE is limited. The reported failed treatment with midazolam ranges between 14 to 18% . [29] , [30] . In the series of Claassen and colleagues acute treatment failure occurred in 18% of episodes, breakthrough seizures in 56%, post treatment seizures in 68% and ultimate treatment failure in 18%. The authors suggest that titrating continuous intravenous midazolam to burst suppression, more aggressive treatment with concurrent AED or a longer period of initial treatment may reduce the high proportion of patients with RSE who relapse after midazolam is discontinued. In this series only 24% had an immediate and sustained response.

Other Pharmacological treatment:

High dose phenobarbital:

High dose of phenobarbital with serum levels of 100 to 200 ug/ml, has been found effective and safe in the treatment of RSE in children. In another study a very high dose phenobarbital at accumulated daily doses up to 80 mg/kg, with a resulting serum level of more than 1000 mumol/l has been shown to effective in achieving seizure control in

children with RSE. In this study the adverse effects were milder compared with thiopental infusion.

Ketamine:

Ketamine, a NMDA antagonist, has been proved useful in RSE[31] and it is also a neuroprotective. However, because ketamine can raise intracranial pressure, the absence of intracranial mass lesion should be confirmed by neuroimaging. The experience with this agent in RSE is very limited.

Inhalational Anesthetics:

Inhalational anesthesia (IA) is an alternative approach to the treatment of RSE. Its attractive feature include efficacy, rapid onset of action and the ability to titrate the doses according to the effects demonstrated on the EEG.[32] Of the various agents, isoflurane and desflurane are the two agents that have been administrated for RSE because of their safety associated with long-term administration.[33] In a recent retrospective study, seven patients with RSE were initiated to IAs (all patients to isoflurane and one patient in addition to desfluratne) after 1 to 103 (mean,19) days. They received multiple AEDs (mean 10, range 7 -15) in addition to IAs. Regardless of seizure type, isoflurane and desflurane consistently stopped epileptic discharges with adequate, sustained electrographic burst suppression within minutes of initiating IA therapy. Four patients had good outcomes. Prolonged use of IAs is well tolerated.[33]

Newer AEDs:

The use of newer AEDS in the treatment of RSE has not been studied systematically. In 6 patients with RSE unresponsive to sequential trials of multiple agents, a suspension of topiramate administered via nasogastric tube was effective in aborting RSE. Effective dosages ranged from 300 to 1,600 mg/d.[34] RSE was terminated in three children with topiramate loading, 5 mg/kg/day.[35] Seizure control has been achieved in patients with RSE by administration of levetiracetam (500-3000 mg/day) by nasogastric route.[36] Injectable levetiracetam formulation is available and the pharmacokinetics of levetiracetam administered by IV infusion was comparable across all dose groups and infusion rates and the pharmacokinetic profile was consistent with that for levetiracetam administered orally.[37] Well designed studies are needed to determine the place of newer AEDs as the use of drugs can avoid pharmacologic coma.

Target of treatment-burst suppression:

Experimental studies demonstrated maximal depression of cerebral metabolism with barbiturates with burst suppression intervals of 30 seconds.[38] Burst suppression and isoelectric background EEG have been shown to be accompanied by fewer recurrent seizures than simply stopping seizures. There is uncertainty about the optimal extent of EEG suppression in RSE. Several authors used different burst suppression intervals. Kofke *et al*[39] used 15 to 30 seconds as burst suppression interval. Van Ness used 3 to 9 bursts per minute during pentobarbital treatment. Mirsattari and colleagues[33] considered the maintenance of burst suppression for burst duration of less than 1 second

and suppression duration longer than 10 seconds as the goal of therapy. Where as Bleck advocates a more aggressive approach using isoelectric EEGs. In a recent retrospective study the outcome was independent of the extent of EEG burst suppression and probably related to the underlying cause of RSE.

Maintenance therapy:

In parallel with emergency treatment attention must be given to maintenance AED therapy to prevent recurrence of seizures. In patients known to have epilepsy, their usual AEDs should be maintained and dose adjustments may be required depending on AED levels. In patients presenting *denovo* the AEDs, phenytoin/fosphenytoin or valproate, used to control the status can in principle be continued as oral maintenance therapy. In others, unless relatively short-lived treatment is anticipated, the preference is to initiate oral maintenance therapy, valproate or carbamazepine, starting immediately at standard doses.[40] If additional medication is needed, the most appropriate AEDs are topiramate and levetiracetam as these drugs can be started at high doses with a low risk of idiosyncratic reactions.[41]

REVIEW OF LITERATURE

A retrospective cohort ctudy was conducted by Stephen et al[42] in the neurological intensive care unit (NICU) at Columbia-Presbyterian Medical Center between January 1, 1994, and March 31, 1998 to determine the frequency, risk factors, and impact on outcome of RSE. Consecutive sample of 83 episodes of status epilepticus in 74 patients were studied. In 57 episodes (69%), seizures occurred after treatment with a benzodiazepine, and in 26 (31%), seizures occurred after treatment with a second-line anticonvulsant drug (usually phenytoin), fulfilling our criteria for RSE. Nonconvulsive SE (P= .03) and focal motor seizures at onset (P= .04) were identified as independent risk factors for RSE. Eleven (42%) of 26 patients with RSE had seizures after receiving a third-line agent (usually phenobarbital). Although mortality was not increased (17% overall), RSE was associated with prolonged hospital length of stay (P<.001) and more frequent functional deterioration at discharge (P= .02). They concluded that refractory status epilepticus occurs in approximately 30% of patients with SE and was associated with increased hospital length of stay and functional disability. Nonconvulsive SE and focal motor seizures at onset were risk factors for RSE.

M Holtkamp et al[43] retrospectively analysed all episodes of status epilepticus (SE) treated between 1993 and 2002 on the neurological intensive care unit (NICU) of the Charité-Universitätsmedizin Berlin. The predictive and prognostic features of RSE were compared with non-RSE (NRSE). All patients with “de novo” SE were followed

up to identify the possible development of post-SE symptomatic epilepsy. A total of 83 episodes fulfilled their criteria of SE. Of these 43% were refractory to first line anticonvulsants. The mean age of patients with SE was 53.3 (SD 19) years, with only two patients younger than 18 years. Encephalitis was significantly more often the primary cause in RSE ($p<0.05$), whereas low levels of antiepileptic drugs were significantly more often associated with NRSE ($p<0.001$). Hyponatraemia within the first 24 hours after onset of status activity was significantly more often associated with RSE ($p<0.05$). In RSE, compared with NRSE, significantly longer duration of seizure activity ($p<0.001$), more frequent recurrence of epileptic activity within the first 24 hours after the end of seizure activity ($p<0.001$), longer stay in the NICU and in hospital ($p<0.001$ and $p<0.01$, respectively), and more frequent development of symptomatic epilepsy ($p<0.05$) were seen. SE treated in the NICU was frequently refractory to first line anticonvulsant drugs. Encephalitis was a predictor for RSE, which was associated with markedly poor outcome, in particular, the development of post-SE symptomatic epilepsy.

In a prospective study conducted by Ramon Rivera, Miguel Seginini et al [44], 24 children diagnosed with the diagnosis of status epilepticus were admitted and treated in the Intensive Care Unit, National Children's Hospital, Costa Rica with midazolam infusion. Out of 24 patients, 10 were male and 14 were female. The mean age was 2.2 yrs (range 2 months to 12 yrs). Fourteen patients had history of epilepsy and were in anticonvulsants prior to admission (phenobarbital (n=6), phenobarbital plus phenytoin

(n=4) and carbamazepine (n=4)). But at the moment of admission, the serum levels of these drugs are not known. The other ten patients presented at the emergency room with their first conclusive episode. Four patients had infection of central nervous system. Six had idiopathic epilepsy. Majority of patients (n=18) had generalized tonic-clonic seizures, followed by focal seizures (n=6) and focal with secondary generalization (n=1). The mean time between admission to the emergency room and the establishment of midazolam infusion was 0.75 hrs (range 0.25 to 2.5 hrs). Complete arrest of seizures was achieved with midazolam therapy in all 24 patients. The mean infusion rate of midazolam necessary to control the fits was 2.3 µg/kg/min. (range 1 to 18). They observed that none of the patients experienced clinically important changes in blood pressure or respiratory status while receiving midazolam as an intravenous infusion. In addition, none of the patients required endotracheal intubation and assisted ventilation. The metabolic parameters were within normal limits and all of them regained full consciousness at a mean time 4.2 hrs (range 2 to 8.5 hrs) after discontinuation of the midazolam infusion. They concluded that midazolam is an effective and safe therapeutic approach for the management of pediatric patients with status epilepticus.

In another interesting study conducted by Roshan Lal Koul, Raj Ajithala G et al [45] as in a tertiary referral centre in Sultanate of Oman, 20 children with status epilepticus were admitted of which majority were males (n=15) and the rest (n=5) were females. The mean age was 4.07 yrs (range 2 months to 13 yrs). Eleven children had history of seizures and were already taking anticonvulsants, eight children had idiopathic

epilepsy, three had acute purulent meningitis, three had acute meningo encephalitis and the remaining had various vascular or degenerative lesions of the brain. Majority presented with generalized tonic clonic seizures (n=13), four children had partial seizures, myoclonic status in one child and Lennox-Gastaut status in two children. Twelve patients had refractory status epilepticus. Complete arrest of seizures was achieved with midazolam infusion in all but one child who had Batten's disease. The mean time to control seizures in refractory status epilepticus was 64.6 minutes (range 15-240 minutes) and in established status epilepticus 34.3 minutes (range 10-60 minutes). The mean time between start of midazolam infusion and total cessation of seizures in all patients was 54 minutes. The mean infusion rate of midazolam required to control the seizures completely was two µg /kg/min (range 1-5 µg/kg/min). Only two children had transient fall in oxygen saturation (to 90%) as demonstrated by pulse oxymetry however, none of the patients required mechanical ventilation and none showed any abnormalities in electrolyte and glucose levels. So this study too suggested that midazolam infusion is an effective and safe therapeutic approach for refractory status epilepticus (RSE).

The meta-analysis conducted by Donald L. Gilbert, Peter S. Gartside [46] in 1999 was the first study that systematically analyzed the published literature on the treatment of refractory generalized convulsive status epilepticus in children. One hundred eleven children from 12 articles published between 1983 and 1998 met their inclusion criteria.

Five drugs (midazolam, pentobarbital, thiopental, isoflurane and diazepam) were used in patients who met inclusion criteria. They found that midazolam, pentobarbital, thiopental and isoflurane were 100% efficacious, in an average of less than 1 hour after starting treatment. The only treatment failures were seen in diazepam study in which seizures continued in 14% of children. The efficacy of all treatments in symptomatic cases was 92% versus 96% in idiopathic cases (p=0.42). The overall mortality in children treated for refractory generalized convulsive status epilepticus was 16%. Mortality in children with symptomatic etiologies was significantly greater than that in idiopathic group (1 of 27; Fisher's exact test; p=0.033). The overall mortality rate in children treated with diazepam was 19%; with isoflurane 40%, with pentobarbital 17% and with thiopental was 31%. But there were no deaths among children treated with midazolam. The incidence of new neurological defects was 25% in the midazolam studies. With the apparent effectiveness of midazolam in children with refractory generalized convulsive status epilepticus, they suggested that midazolam should be considered as first line therapy for treatment of refractory status epilepticus.

Minagawa K, Yanai s [47] reviewed 48 episodes of refractory status epilepticus in children. The mean age of patients was 3.5 years (range 1 month to 18 years). Nine children had epilepsy, one purulent meningitis, one encephalitis, one acute hypoxic ischemic encephalopathy. The types of seizure were generalized tonic clonic seizures in 41 episodes, a tonic seizure in 3, an atypical absence in 1 and a complex partial seizure

in 3 children. All patients were treated with midazolam infusion after a bolus dose. Forty one of the 48 episodes of seizures were controlled within 30 minutes after initiation of midazolam therapy. The mean infusion rate of midazolam required was 0.22 mg/kg/hr. The duration of treatment was 4.1 days. None of the patients had serious changes in the blood pressure or respiratory status attributable to the use of midazolam infusion. They concluded that midazolam infusion is an effective and safe therapeutic approach for the management of childhood status epilepticus.

Parent JM, Lowenstein DH in their study [48] comprising of four patients with refractory generalized status epilepticus, who were monitored by electroencephalogram, documented the cessation of seizure activity within minutes of the loading dose in all the patients. No adverse effects occurred during midazolam treatment. Only one patient required fluid boluses and pressure support for hypotension while the remainder of the patients safely tolerated midazolam despite preexisting hemodynamic instability. All the patients had recovered and maintained good seizure control.

In an Indian study done by Singhi S, Murthy A et al., at Chandigarh, they compared the efficacy of continuous midazolam versus diazepam infusion in RSE [49]. It was an open-label, randomized control study at their Intensive Care Unit. The subjects included 40 children, 2 to 12 years of age with refractory status epilepticus. Either continuous midazolam (n=21) or diazepam infusion (n=19) in incremental doses was administered for seizure control. The two groups were similar in age (mean ± SD = 4.9 ±43.6 months) and etiology. Twenty three (57.5%) of patients had acute central nervous

system infection. RSE was controlled in 18 (86%) and 17 (89%) patients in the midazolam and diazepam groups respectively (p=not significant). They found that the median time to control seizures was 16 minutes in both the groups, but in the midazolam group, seizures recurred in more children (57% versus 16% in diazepam group; $p< 0.05$). The maximum dose (mean ±SD) of midazolam and diazepam required was 5.3±2.6 µg/kg/min and 0.04±0.02 mg/kg/min, respectively. About half of the patients needed mechanical ventilation and 40% had hypotension in both groups but they found that the mortality was higher in the midazolam group (38%) as compared to the diazepam group (10.5 %, $p< 0.01>0.05$). They concluded that continuous midazolam and diazepam infusions were equally effective for control of RSE. However, midazolam was associated with more seizure recurrence and higher mortality in RSE predominantly caused by central nervous system infections.

In a small retrospective study comprising of seven patients with refractory status epilepticus done by Kumar A, Bleck TP [50], they found that midazolam infusions terminated status epilepticus in all patients in less than 100 seconds as determined by clinical observation (three patients) or electroencephalographic monitory (four patients). But all the patients received mechanical ventilation before receiving midazolam. They found that one patient developed mild hypotension. In this small study, they concluded that midazolam appears to be an effective and safe alternative to high dose barbiturate coma for the termination of status epilepticus when conventional agents have failed.

STUDY JUSTIFICATION

Identification of predictors for RSE is crucial for detection of patients at risk early in the course of the disease.Despite its frequency, little is known about the predictive and prognostic features of the critical condition of RSE.The clinical characteristics of refractory status is poorly understood and therefore the current management approaches are still unsatisfactory.Refractory status epilepticus (RSE) is a condition in search of improved clinical characterisation and more efficient treatment options. In contrast with status epilepticus (SE) in general, only a few studies have been reported on the subgroup of refractory status and moreover there are very few studies of RSE in childhood.

AIMS AND OBJECTIVES

- To determine the predictors of refractory status epilepticus

- To monitor the complications and impact on outcome of refractory status epilepticus

MATERIALS AND METHODS

STUDY DESIGN:

Case – control study

STUDY PERIOD:

October 2007- September 2009

STUDY PLACE:

Institute of child health and hospital for children,Egmore.

STUDY POPULATION:

INCLUSION CRITERIA:

Continuous seizure activity lasting for more than 30 minutes or intermittent seizure activity without recovery of consciousness in between the episode in children aged between 1 month to 12 years.

EXCLUSION CRITERIA:

(1) Age < 1 month

(2) Children with seizures only at home.

(3) Children with head injury

(4) Children in case group of RSE in whom first line anticonvulsants were not given sequentially before starting midazolam.

CASE DEFINITION:

Cases with seizures lasting beyond treatment with a benzodiazepine and second line intravenous anticonvulsant drug(phenytoin and phenobarbitone).

CONTROL DEFINITION:

Cases with seizures responding to benzodiazepine and a second line intravenous anticonvulsant drug (phenytoin or phenobarbitone).

LIMITATION:

- Serum levels of anticonvulsants were not known during admission
- Electroencephalographic monitoring was not available

CONSENT:

Institutional consent was obtained from the parents after explaining the nature of study.

MANOEUVRE:

One hundred and eleven children between the age group of 1 month to 12 years admitted in our hospital with the diagnosis of refractory status epilepticus were included in the study group and one hundred children between the age group of 1 month and 12 years admitted in our hospital with status epilepticus were included in control group in our study.

Status epilepticus was diagnosed when child had continuous seizure lasting more than 30 minutes or several seizures occurring without regaining consciousness between the seizure activity. These children were treated with 0.1 mg/kg of lorazepam 2 doses, 20mg/kg loading dose of phenytoin followed by 10 mg/kg half loading dose of phenytoin and 20 mg/kg loading dose of phenobarbitone at predetermined time interval in succession after stabilizing the airway, breathing and circulation. Intubation was done prior to phenobarbitone administration. Refractory status epilepticus was the diagnosis if the child continued to have seizure activity despite adequate doses of medications mentioned above.

A thorough history was obtained from the parents regarding name, age, sex, area, duration of seizure prior to reaching hospital, type of seizure , presence or absence of fever. Past history of seizure / status epilepticus and the anticonvulsant drug and dose (whether adequate) and any history of drug default or any recent change in anticonvulsant drug was enquired and noted down. Any history of drug or toxin ingestion , family history of status epilepticus or febrile seizure was

enquired. Presence of any neurological co morbidity and its type if present , was enquired in detail.

Total time taken to control the seizure , number of drugs required , whether ventilator support was required was noted down. The complications during status epilepticus and the consciousness and neurological status at the end of status epilepticus were recorded. Later the patients were followed up in the ward for any recurrence of seizure , time taken for complete control of seizure. A thorough clinical examination was carried out including monitoring of vitals, oxygen saturation and systemic examination to find out the cause, if any, involving the central nervous system, cardiovascular system, renal and respiratory system.

Complete blood count, liver function test,renal function test and chest X ray were done in all patients. In order to exclude electrolyte and metabolic disturbances as a cause or complication of seizures , blood samples were taken for electrolytes, glucose and calcium estimation. Mantoux, resting gastric juice for Acid fast bacilli, cerebrospinal fluid analysis ,cerebrospinal fluid lactate and pyruvate were done if indicated. Computed tomography of brain was done in all patients. Magnetic resonant imaging of brain was done in selected cases. Final diagnosis of various underlying problems was made based on the clinical history, physical examination and various investigation.

The patients were further followed up for any complications acquired during

hospital stay, duration of ventilation required length of stay in hospital stay. The neurological status of the child at the time of discharge was noted.

All statistical analysis (mean, median, standard deviation) was done using SPSS version 11 for windows and data were statistically analysed, compared and interpreted.

OBSERVATIONS

A total of 111 children in case group with refractory status epilepticus and 100 children in control group with non refractory status epilepticus were studied.

The age distribution is as follows:

TABLE – 1

Age distribution

Age	Case group	Control group
< 1 yr	27(24.3%)	21(21%)
1 – 5 yrs	28(25.2%)	23(23%)
5 – 9 yrs	24(21.6%)	29(29%)
9 – 12 yrs	32(28.8%)	27(27%)

The percentage of RSE cases was comparable in all the age groups.The number of RSE cases in children <1 year was 27(24.3%) with an insignificant p value of 0.565 and Odds ratio of 1.209 . This is in contrast to the previous studies which concluded <1 year as a risk factor for RSE. The youngest child in the study group was 2 months and the child with maximum age in study group was 12 yrs. The commonest age group in this study was 9 – 12 yrs with 32 cases (28.8%).

The sex distribution is as follows:

TABLE- 2

SEX DISTRIBUTION

SEX	CASES	CONTROL	TOTAL
MALE	61(55%)	57(57%)	118(55%)
FEMALE	50(45%)	43(43%)	93(45%)

The total number of male patients in the study was 118(55%), with 61 in the RSE group and 57 in the control group. The total number of female patients in the study was 93(45%), with 50 in the RSE group and 43 in the SE group. Not either of the sex had a significant p value and so neither were found to be a risk factor for RSE.

TABLE – 3

Duration of seizure prior to reaching hospital

Vast majority of the patients with RSE were brought to the hospital more than 60 min after onset of seizure, with the exact number being 51 in RSE group and 30 in NRSE group with a p value of 0.015 which is significant and an odds ratio of 2.1 . The median duration of seizures before reaching the hospital was 40 minutes and standard deviation was 38.12 minutes. Minimum time of seizures before reaching hospital was 10 minutes while the maximum time was 90 minutes. Long duration of seizure prior to reaching hospital was found to be a risk factor for RSE.

TABLE- 4

TYPE OF SEIZURE

Type of seizure	Cases	Control	p value	Odds ratio	95% confidence interval
Focal to GTCS	26(23.4%)	11(11%)	0.018	2.475	1.152-5.319
GTCS	85(76.6%)	89(89%)			
Total	111	100			

Majority of the patients in both the groups had generalized tonic clonic seizures numbering 85 in RSE group and 89 in NRSE group. However focal to secondary generalization was more associated with RSE than NRSE with a Chi square value of 5.615 and a significant p value of 0.018 and an odds ratio of 2.475 with 95% confidence interval being 1.152- 5.319. This result goes hand in hand with the observation made by Stephan et al that focal onset of seizure was a major risk factor for RSE.

TABLE-5

Past history of status epilepticus

Past H/O Status epilepticus	Cases	Control
Yes	7(6.3%%)	6(6%)
No	104(93.7%)	94(94%)
Total	111	100

7 patients among RSE group had previous history of status epilepticus as against 6 in NRSE group. Among this 7 in RSE group 2 patients had primary seizure disorder and 5 were cerebral palsy children with seizures. Among this 6 in NRSE group 1 patient had primary seizure disorder and 5 were cerebral palsy children with seizures. Past history of status epilepticus was not a risk factor for RSE and had an insignificant p value.

TABLE-6

Drug withdrawal

Withdrawal	Cases	Control	p value	Odds ratio	95% confidence interval
Yes	27(71%)	7(26%)	0.001	6.6	3.56-13.62
No	11(29%)	19(74%)			
Total	38	26			

38 patients in RSE group had seizure disorder out of which 5 had primary seizure disorder, 20 were cerebral palsy children with secondary seizure disorder and 3 were post meningitic/encephalitic sequelae with secondary seizure disorder. 7 patients in NRSE group had seizure disorder out of which 2 had primary seizure disorder,4 were cerebral palsy children with secondary seizure disorder and 1 was a post meningitic/encephalitic sequelae with secondary seizure disorder. Drug withdrawal had a significant association with RSE with a p value of 0.001 and odds ratio of 6.6 and 95% confidence interval of 3.56-13.62

TABLE-7

Inadequate drug dose

Dose inadequate	Case	Control	p value	Odds ratio	95% confidence interval
Yes	18(47.3%)	5(19.2%)	0.031	3.78	1.82-7.42
No	20(52.7%)	21(80.8%)			
Total	38	26			

18 patients in RSE group had a history of drug withdrawal as against 5 in NRSE group. Among the 18 with history of drug withdrawal in RSE group 2 had primary seizure disorder,15 were cerebral palsy children with secondary seizure disorder and 1 was a post meningitic/encephalitic sequelae with seizure disorder. Among the 5 with history of drug withdrawal in NRSE group 1 had primary seizure disorder,3 were cerebral palsy children with secondary seizure disorder and 1 was a post meningitic/encephalitic sequelae with seizure disorder. History of drug withdrawal was associated with RSE with a significant p value of 0.031 .

Table-8

Recent change in AED

Recent change in AED	Cases	Control	p value	Odds ratio	95% confidence interval
Yes	6(15.7%)	3(11.5%)	0.083	1.4	0.81-2.91
No	32(84.3%)	23(88.5%)			

Total	38	26			

6 patients in RSE group had a history of recent change in AED as against 3 in NRSE group. Among the 6 with history of drug withdrawal in RSE group 2had primary seizure disorder,4 were cerebral palsy children with secondary seizure disorder and. Among the 3 with history of drug withdrawal in NRSE group 1 had primary seizure disorder,2were cerebral palsy children with secondary seizure disorder. History of recent change in AED was significantly associated with RSE with a p value of 0.031 .

Table-9

Neonatal seizure among children with CP

NNS among children with CP	Case	Control	p value	Odds ratio	95%confidence interval
Yes	19(63.3%)	3(20%)	0.003	6.9	3.92-13.12
No	11(36.67%)	12(80%)			
Total	30	15			

19 cerebral palsy patients out of 30 in the RSE group had a prior history of neonatal seizure and 3 cerebral palsy patients out of 15 in the NRSE group had a

prior history of neonatal seizure. History of neonatal seizure among cerebral palsy children had a significant association with RSE with a p value 0.003

Table-10

Shock in E- Room

Shock	Case	Control
Present	111(100%)	85(85%)
Absent	0	15(15%)
Total	111	100

All the 111 patients in RSE group had shock that was managed in Emergency Room with fluid boluses followed by inotropes if necessary. 85(85%) patients in control group had shock.

Table -11

Recurrence of seizure after control of status epilepticus

Recurrence	Case	Control	p value	Odds ratio	95% confidence interval
Yes	20(18%)	7(7%)	0.017	2.92	1.178-7.239
No	91(82%)	93(93%)			
Total	111	100			

Recurrence of seizure after control of status epilepticus was seen in 20 patients in RSE group as against 7 in NRSE group with a p value of 0.017 and

odds ratio of 2.92

Table-12

Ventilator support

Ventilator support	Cases	Control
Yes	104(93.7%)	48(48%)
No	7(6.3%)	52(52%)
Total	111	100

104(93.75%) patients in RSE group required ventilator support. In the remaining 7 patients phenobarbitone and midazolam infusion was started in ward and these cases were not intubated.

Table -13

Duration of ventilator support

Duration of ventilator support	Case	Control
<1 day	17(16.3%)	18(37.5%)
1-5 days	40(38.5%)	22(45.8%)
>5 days	47(45.2%)	8(16.7%)
Total	104	48

47 patients in RSE group required ventilator support for a longer period as against 8 in NRSE group. Patients in RSE group required longer duration of ventilator support than the NRSE group.

Table -14

Complications during hospitalization

Complication	Case	Control
Pneumonitis	58(52.3%)	29(29%)
Refractory shock	10(9%)	3(3%)
UTI	9(8.1%)	10(10%)
Renal failure	2(1.8%)	0(0%)
Sepsis	4(3.6%)	1(1%)

Pneumonitis 58 (52.3%) was the common complication among children with RSE. Refractory shock was seen in 10(9%) of RSE cases. UTI was seen in 9(8.1%) of RSE cases. Even in NRSE group pneumonitis was the common complication observed.

Table -15

CT changes

Change seen	Case	Control
Normal	55(49%)	74(74%)
Cerebral edema	20(18%)	9(9%)
Hydrocephalus	5(4.5%)	2(2%)
Calcification	4(3.6%)	2(2%)
Infarct	3(2.7%)	0
Haemorrhage	2(1.8%)	0
Gliosis	2(1.8%)	2(2%)
HIE changes	5(4.5%)	3(3%)
Neuronal migration disorder	8(7.8%)	3(3%)
Porencephaly	3(2.7%)	2(2%)
SOL	2(1.8%)	2(2%)
REL	2(1.8%)	1(1%)

Abnormal CT scan was reported in 56(51%) cases in RSE group as against 26(26%) in NRSE group. The association between abnormal CT findings and RSE is significant and has a p value of 0.001. CT scan was done in all the cases in both the case and control group.

Table -16

MRI changes

Changes seen	Cases	Control
Normal	6(27%)	5(62.5%)
Cerebral edema	6(27%)	1(12.5%)
Hydrocephalus	0	0
Calcification	1(4.5%)	0
Infarct	3(14%)	0
Haemorrhage	2(9%)	0
Demyelination	1(5%)	1(12.5%)
Neuronal migration disorder	0	0
HIE changes	0	0
Porencephaly	0	0
SOL	2(9%)	1(12.5%)
REL	1(4.5%)	0

MRI was done only in selected cases. Out of the 22 cases in RSE group MRI was abnormal in 16 cases and out of the 8 cases in control group MRI was abnormal in 3 patients.

Table – 17

Etiology

Etiology	Cases	Control	p value	Odds ratio	95% confidence interval
CNS infection	35(31.5%)	15(15%)	0.005	2.61	1.323-5.148
Seizure disorder	15(13.5%)	20(20%)	0.206	0.625	0.301-1.3
CP	30(27%)	15(15%)	0.033	2.099	1.052-4.186
Febrile seizure	10(9.7%)	40(40%)	0.0731	1.2	0.501-2.8
CVA	5(4.6%)	0	0.032	-	-
SOL	2(1.8%)	1(1%)	0.623	1.817	0.162-20.343
Hypertensive encephalopathy	2(1.8%)	1(1%)	0.0623	1.817	0.162-20.343
Metabolic	1(0.9%)	0	0.341	-	-
Neurodegenerative disorder	3(2.71%)	1(1%)	365	2.75	0.281-26.874
Toxins	3(2.7%)	0	0.098	-	-
PES/PMS	5(4.6%)	7(7%)	0.434	0.621	0.192-2.041

CNS infection was the most common cause of RSE accounting for 31.5% of cases in the RSE group with a p value of 0.005. However CNS infection was the cause in only 15% of the cases in NRSE group. CNS infection was followed by CP as the next common cause for RSE accounting for 27% of the cases and a significant p value of 0.033 . All the patients with cerebrovascular accident and

toxin ingestion had RSE. Febrile seizure was the most common cause for NRSE accounting for 40% of cases in the control group.

Table-18

Precipitating factor

Precipitating factor	Case	Control	p value	Odds ratio	95% confidence interval
Fever	54(48.6%)	49(49%)	0.959	0.986	0.572-1.693
Poor compliance	30(27%)	13(13%)	0.012	2.479	1.209-5.081
Lack of sleep	4(3.6%)	3(3%)	0.807	1.209	0.264-5.537
Stress	4(3.6%)	3(3%)	0.807	1.209	0.264-5.537

Fever was the precipitating cause for seizure in 48.6% of cases in RSE group and 49% of cases in NRSE group. Poor drug compliance was the precipitating factor in 27% of cases in RSE group and 13% of cases in NRSE group with a significant association with RSE with a p value of 0.012 . Lack of sleep and stress were the precipating factor in 3.6% and 3% of patients in RSE and NRSE group respectively.

Table-19

Outcome

Outcome	Case	Control	p value	Odds ratio	95% confidence interval
Recovered normally	36(32.4%)	59(59%)	0.87	0.33	0.172-0.782
Recovered with fresh weakness	33(29.7%)	18(18%)	0.045	1.9	1.01-4.012
Recovered with no fresh deficit	20(18%)	11(11%)	0.3	1.93	1.04-4.013
Mortality	25(22.5%)	12(12%)	0.038	2.13	1.23-4.62

32.4% of patients with RSE recovered without any weakness and 59% of patients in NRSE group recovered without weakness. Fresh deficit was seen in 29.7% of cases in RSE group compared to 18% in NRSE group. Mortality was higher in RSE group with 22.5% of patients succumbing to illness.

Table-20

Risk factor for refractory status epilepticus as derived by Univariate Logistic Regression analysis

Table- 21

Risk factors for refractory status epilepticus as derived by multiple logistic regression analysis

Among the various risk factors which were analysed previously by univariate analysis, focal onset of seizure (OR(95% C.I) = 2.1234 (1.012-4.239)), drug withdrawal (OR(95% C.I) = 8.5909 (1.574-46.88)) , prolonged duration of seizure prior to hospitalization (OR(95% C.I) = 0.012(1.701-6.54)) , history of neonatal seizure among children with CP(OR(95% C.I) = 13.1429 (0.8687-60.2)), abnormal neuroimaging (OR(95% C.I) = 4.3293 (2.0877-8.97)), acute CNS infection (OR(95% C.I) = 2.2368 (1.118-4.47)), were found to be the independent risk factors f or refractory status epilepticus by multiple logistic regression analysis.

DISCUSSION

This case-control study was conducted to study the risk factors for refractory status epilepticus and its impact on outcome of the patient.

Table-20

Comparison of age and sex distribution with other studies

	Mean age	Range	M:F
Present study	5.91yrs	2mo-12yrs	1.06:1
Roshan la et al.,[45]	4.07yrs	2mo-13ytr	3:1
Ramon rivera et al.,[43]	2.2yrs	2mo-12yrs	1:1.4
John Igartua et al.,[51]	4.25yrs	17days-16yrs	-
Minagawa K,at al.,[47]	3.5yrs	1mo-18yrs	-

The mean age of children in our study was 5.91years, while in the study by Roshan Lal et al was 4.07 years and2.2 years in study by Ramon Rivera et al. The mean age was 3.5 years and 4.25 years in studies by Minagawa K et al.,and John Igartua et al. Less than 1 year as a risk factor for RSE as made out in the study by Col.M.K.Behera et al was not a risk factor in this present study.There was no clustering of cases in any age group. So age was not a risk factor for refractory status epilepticus. The ratio of male to female in the present study was 1.06:1 which is comparable to the study done by Ramon rivera et al ., in which it was

1:1.4. higher incidence in males (3 times more) was noticed in study by Roshan Lal et al.

Table-21

Comparison of seizure type with other studies

Seizure type	Present study	Stephen et al[42]	Roshan Lal et al[45]	Ramon Rivera et al[44]	John Igartua et al[51]
GTCS	76.6%	23%	65%	755	62.55
Partial to GTCS	23.4%	73%	20%	4.2%	25%

Though 76.6% of the patients had GTCS in the present study, focal to secondary generalization was more associated with RSE with a p value of 0.018 in univariate analysis and a p value of 0.042 in multiple logistic regression. A similar observation has already been made in the study by Stephen et al.

6.3% of patients in the present study with RSE had prior history of status epilepticus as against 6% in the NRSE group with an insignificant p value. No previous studies are available to compare this as a risk factor.

Duration of seizure prior to hospitalization was >60 minutes in 46% of patients in RSE group compared to 30% in NRSE group with a significant p value of 0.012 in multiple logistic regression . Prolonged duration of seizure prior to hospitalization was a risk factor for RSE , similar to the observation made by Ramon Rivera et al ., where the mean time was 0.75 hours.

38 patients in the RSE group and 26 patients in NRSE group had seizure

disorder. Drug withdrawal was a cause of RSE in 71% of the patients in RSE group with a significant p value of 0.001in univariate analysis and a p value of 0,0130 in multiple logistic regression . Inadequate drug dose as a cause of RSE was seen in 47.3% of patients in RSE group as against 19.2% in the NRSE group and this as a risk factor for RSE had an insignificant p value of o.8106 in multiple logistic rregression .

History of neonatal seizure among children with CP was observed in 63.3% of RSE group compared to 20% in NRSE group with a significant p value of 0.0009 in multiple logistic regression. This result is similar to the observation made by Yoko Ohtsuka et al where100% of refractory cases with CP had a history of neonatal seizure.

Recurrence of seizures after control of status epilepticus was seen in 18% of cases in RSE group as against 7% in NRSE group with a significant p value of 0.017. A similar result of recurrence of seizure in 57% of cases of RSE was observed in a study conducted by Singhi S. et al.

Ventilatory support was required in 93.7% of patients in RSE group as against 48% in NRSE group. 50% of patients with RSE required ventilator support in a study by Shinghi S et al. Most of the patients requiring ventilation in RSE group required it for longer duration.

Pneumonitis was the common complication seen in 52.3% RSE patients

followed by refractory shock (9%) and urinary tract infection (8.1%)

Abnormal neuroimaging (including CT and MRI) was seen in 63.03% of patients in RSE group. CT alone was abnormal in 51% of patients in RSE group as against 74% in NRSE group. Abnormal neuroimaging as a cause of RSE had a significant p value of 0001 in multiple logistic regression analysis.

CNS infection (31.5%) was the most common etiology of RSE with a significant p value of 0.0227 in multiple logistic regression analysis.This was followed by CP(27%), however it had an insignificant p value of 0.3266 in multiple logistic regression analysis. A similar observation has been made by M. Holtkamp et al., where CNS infection had significant association with a p value of <0.05 .

Children with RSE had a significantly longer duration of hospital stay and longer duration of stay in intensive care unit.

Fever was the precipitating factor in 48.6% of cases in RSE and 49% of cases in NRSE group. Poor drug compliance was observed in 27% of cases in RSE group as against 13% in NRSE group. Poor drug compliance had a significant association with RSE with a p value of 0.012 .

32.4% of patients in RSE group recovered normally as against 59% in NRSE group. 29.7% of patients in RSE group developed fresh weakness as against 18% in NRSE group with a significant p value of 0.045 . There was mortality in 22.5% of patients in RSE group as against 12% in NRSE group with a significant p value of 0.038 . Singhi S et al observed that there was death in 38% of cases with RSE.

SUMMARY AND CONCLUSION:

In this study the following factors were found to be significantly associated with refractory status epilepticus

- Focal onset of seizures
- Withdrawal of antiepileptic drugs in patients with seizure disorder
- Past history of neonatal seizure among patients with cerebral palsy
- Prolonged duration of seizure prior to treatment
- Abnormal neuroimaging
- Acute CNS infection

Seizure recurrence after control of status epilepticus was more observed in patients with refractory status epilepticus.

Ventilator support was required for more patients with refractory status epilepticus and they required it for a longer period.

Pneumonitis was the most common complication seen in patients with refractory status epilepticus followed by refractory shock.

Most of the patients with refractory status epilepticus recovered with weakness.

Mortality was higher in patients with refractory ststus epilepticus.

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ANNEXURE

STATUS EPILEPTICUS

Reg .No:

1. Name :

2. Age :

3. Sex : 1. Male
   2. Female

4. Address :

5. Area: : 1. Rural
   2. Urban

6. Nature of ailment requiring admission : 1. First admission for SE
   2. Admitted for other condition, developed SE later
   3. Known case of seizure disorder, come for SE

7. Family history of SE : 1. Present
   2. Absent

8. Family history of febrile seizure : 1. Present
   2. Absent

9. Past history : 1. Meningitis/ Encephalitis
2. Neurosurgical procedure
3. Head injury
4. Known seizure
5. CP
6. CVA
7. Neurocutaneous syndrome
8. Neonatal seizure
9. None

10. Seizure history : 1. Primary SD
2. Secondary SD
3. Already had one or more SE
4. One episode of afebrile fits- no AED
5. Had simple FS
6. Had atypical FS
7. Had febrile SE
8. None

11. H/O change in seizure type during : 1.Yes
2. No
clinical course

12. Past H/O AED : 1. Regular
2. Irregular

3. Not on AED

13. Dose of AED : 1. Adequate

2. Inadequate

3. NA

14.H/O recent change in drug : 1.YES

2.NO

3.NA

15.H/O withdrawal : 1.YES

2.NO

3.NA

16. Type of SE : 1. GTCS

2. Focal simple

3. Non convulsive

4. Focal to GTCS

5. Myoclonic

6. Mixed

17. Status epilepticus : 1. Continuous seizures

2. Intermittent seizures

18. Duration of seizure before admission (in minutes) : 1. <15

2. 15-30

3. > 30

4. NA

19. Total duration of seizure (in minutes) : 1. < 15

2. 15-30

3. 30-60

4. >60

5. NA

20. Emergency treatment upto : 1. Benzodiazepine alone

2. Phenytoin loading dose

3. Phenytoin half loading dose

4. Phenobarbitone loading dose

5. Midazolam infusion

6. Sodium valproate infusion

7. Others

21. Ventilatory support : 1. Not required - improved

2. Not required - dead

3. Required- Imroved

4. Required – dead

22. Type of ventilatory support : 1. Bag/Tube

2. Ventilator

23. Complication during status : 1. Physical injury

2. C-P arrest

3. Fractured bone

4. Shock

5. Respiratory depression

6. Hyperpyrexia

7. Renal failure

8. None

24. Post ictal weakness : 1. Absent

2. Present-recovered

3. Persistent weakness

25. After SE conscious status : 1. Regained consciousness

2. Drousy arousable

3. Deeply unconscious

26. Duration on ventilator : Hrs days

27. Time taken to regain consciousness : Hrs days

28. After SE neurological status : 1. Normal

2. Deficit

3. No fresh deficit

29 Recurrence of seizure after SE : 1. Present

2. Absent

30. No of days taken for complete : Days

control of seizures

31. Consciousness at discharge : 1. Conscious/Independent
    2. Awake/Dependent
    3. Drowsy arousable
    4. Comatose
32. Neurological status at discharge : 1. No deficit
    2. Deficit
    3. No fresh deficit

33. Complications during hospitalisation : 1. Respiratory failure
    2. Fever
    3. Tachycardia
    4. Hypotension
    5. Pneumonia
    6. UTI
34. Length of stay in IMCU : days
35. Length of stay in hospital : days
36. Investigation :
    1. Blood sugar level
    2. Serum sodium level

3. Creatinine kinase level
4. Serum calcium level
5. CSF analysis
    a. Cell count
    b. Protein
    c. Sugar
    d. C/S

6. EEG findings :

7. CT scan :

8. MRI scan :

37. Etiology of SE :
    1. CNS infection
    2. CVA
    3. CP/MR
    4. Hypoxic brain damage
    5. Toxins
    6. Idiopathic seizure
    7. Neurodegenerative disorder
    8. Neurocutaneous syndrome
    9. Low blood sugar

10. Low serum calcium
11. Febrile seizure
12. HT encephalopathy
13. SOL
14. PMS/PES

38. Precipitating factors : 1. Fever/ intercurrent infection
2. Poor compliance with AED
3. Lack of sleep
4. Physical exertion
5. TV watching
6. Mental stress
7. Others

39. Outcome : 1. Recovered normally
2. Recovered with weakness
3. Recovered with movement disorder
4. Decreased cognitive function
5. Behavioural problem
6. No fresh deficit
7. Mortality

40. H/O neonatal seizure	1. YES
	2. NO

ABBREVIATIONS:

1. RSE : Refractory Status Epilepticus
2. NRSE : Non-Refractory Status Epilepticus